

## **REMARKS**

Claims 114-120 and 122-137 were pending in the present application.

Claims 114-119, 123-129, 132, and 135-137 have been amended to clarify the claimed invention.

Claims 114-119, and 135-137 have been amended to delete the recitation of "with which the protein is natively associated." Support for this amendment can be found at page 11, lines 1-12, of the specification. Claim 114 has further been amended to delete one element of the Markush group.

Claims 115, 116, 118, and 119 have been amended to recite specific Nogo activities. Support for this amendment can be found at page 11, lines 20-30 of the specification.

Claim 117 has been amended to delete one element of the Markush group.

Claims 120 and 122 have been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claims in one or more related applications.

Claims 123 to 125 have been amended to delete dependencies from canceled claims.

Claims 126 and 128 have been amended to incorporate limitations of the claims from which claims 126 and 128 depended, such that claims 126 and 128 are now independent claims.

Claim 127 has been amended to replace the trademark FICOLL with a description of the chemical that FICOLL identifies. As shown by attached Exhibit A, which is a print-out of the legal status information for the trademark FICOLL from the U.S.P.T.O. database, FICOLL is a source identifier for copolymers of sucrose and epichlorohydrin that may be used to prepare high density solutions for laboratory use. This amendment does not represent new matter because the trademark inherently identifies the chemical. Claim 127 has further been amended to delete the reference to claim 126. Claim 127 has also been amended to identify the nucleic acid to which the polynucleotide hybridizes as a "second nucleic acid," and to specify that the second nucleic acid "consists of a nucleotide coding sequence which encodes" a Nogo protein of specified sequence. Support for this amendment can be found in the specification at p. 12, line 15; p. 12, lines 19-20; p. 12, lines 24-25, and p. 12, lines 31-35.

Claim 129 has been amended to correct a clerical error. In particular, the recitation of "claims" has been replaced with "claim" because claim 129 depends only from a single claim.

Claim 132 has been amended to replace "a protein encoded by said nucleic acid" with "the protein encoded by said nucleic acid," for proper antecedent basis.

Claim 133 has been canceled without prejudice in order to avoid having a claim refer to two different claims, and to avoid having a multiply dependent claim depend upon a multiply dependent claim. Claim 133 has been replaced with new claim 138.

Claim 134 also has been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of canceled claim 134 in one or more related applications.

Claim 135 has been amended to remove the reference to claim 115 and to delete several elements of the Markush group. Claim 135 has been amended further to re-number the elements of the Markush group. Elements (ii) to (v) have been amended further to clarify that the amino acid sequence consists of the amino acid sequence of SEQ ID NOs: 43-46; support for this amendment can be found at page 15, line 18, of the specification. The fragment of element (vi) has also been amended to recite amino acids 762-1163. Support for this amendment can be found at page 3, line 33, of the specification.

Claims 135, 136, and 137 have been amended to specify that the claim is directed to a protein. Support for this amendment can be found at page 11, lines 11-12, of the specification. Support can further be found at page 33, lines 21-22, which shows that fragments are considered proteins. These claims have further been amended to remove the reference to claim 115. These claims have also been amended to recite that the protein is free of all central nervous system myelin material. Support for this amendment can be found in the specification at page 11, lines 11-12. Claim 136 has also been amended to recite that the protein consists of the listed amino acid sequences. Support for this amendment can be found at page 15, line 17, of the specification. Claim 137 has also been amended to delete several elements of the Markush group and to renumber the remaining elements.

New claims 138-141 have been added. Support in the specification for the new claims can be found as set forth in the chart below.

<u>Claim</u>	<u>Feature</u>	<u>Support</u>
138	An isolated nucleic acid comprising a polynucleotide which	p. 3, <i>ll.</i> 1-5
	(i) hybridizes to a second polynucleotide under high stringency conditions comprising: (a) hybridization in 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA,	p. 13, <i>l.</i> 31 to p. 14, <i>l.</i> 5

<u>Claim</u>	<u>Feature</u>	<u>Support</u>
	0.02% PVP, 0.02% of a copolymer of sucrose and epichlorohydrin, 0.02% BSA, and 100 µg/ml denatured salmon sperm DNA at 65°C; and (b) washing in a solution containing 2X SSC, 0.01% PVP, 0.01% of a copolymer of sucrose and epichlorohydrin, and 0.01% BSA at 37°C for 1 h, and subsequently in 0.1X SSC at 50°C for 45 min;	
	wherein the second polynucleotide consists of a nucleotide coding sequence which encodes the amino acid sequence of SEQ ID NO: 2, amino acids 975-1163 of SEQ ID NO: 2, amino acids 1-171 fused to amino acids 975-1163 of SEQ ID NO: 2, SEQ ID NO: 29, the carboxy-terminal 188 amino acids of SEQ ID NO:29, or amino acids 1-172 fused to the carboxy-terminal 188 amino acids of SEQ ID NO: 29; and	p. 12, <i>l.</i> 13 to p. 13, <i>l.</i> 3
	(ii) encodes a protein, wherein an antibody that binds to the protein also binds to a protein consisting of the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:29.	p. 3, <i>ll.</i> 17-18
139	An isolated protein, wherein the protein (a) is free of central nervous system myelin material; and (b) comprises:  (i) an amino acid sequence consisting of amino acids 31-57 of SEQ ID NO:2; or  (ii) an amino acid sequence consisting of amino acids 1090-1125 depicted in Figure 2a (SEQ ID NO:2).	p. 3, <i>ll.</i> 23-24; p. 11, <i>ll.</i> 1-16; p. 33, <i>ll.</i> 21-22  Original claim 16 <sup>1</sup>  Original claim 16 <sup>2</sup>
140	An isolated protein, wherein the protein (a) is free of central nervous system myelin material; and (b) consists of:  (i) the carboxy-terminal 188 amino acids of SEQ ID NO:29;	p. 3, <i>ll.</i> 23-24; p. 11, <i>ll.</i> 1-16; p. 33, <i>ll.</i> 21-22  p. 8, <i>ll.</i> 3-6 <sup>3</sup> ; p. 15, <i>ll.</i> 11-16; Figure 13; p. 12, <i>ll.</i> 26-27

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<sup>1</sup> The amendment of August 19, 2004 added the language of original claim 16 to the Summary of the Invention at p. 3, *l.* 28, so that support for these fragments can be found in this section of the specification.

<sup>2</sup> See footnote 1 above.

<sup>3</sup> It is noted that the recitation of SEQ ID NO:30 in the specification as filed was amended to recite SEQ ID NO:29 in the Preliminary Amendment under 37 C.F.R. § 1.115 filed October 21, 2002.

<u>Claim</u>	<u>Feature</u>	<u>Support</u>
	(ii) an amino acid sequence consisting of amino acids 988-1023 of SEQ ID NO: 2;	p. 3, <i>ll.</i> 23-28
	(iii) an amino acid sequence consisting of amino acids 975-1162 of SEQ ID NO: 2;	p. 17, <i>ll.</i> 25
	(iv) an amino acid sequence consisting of amino acids 172 to 974 of SEQ ID NO:2;	p. 10, <i>ll.</i> 1-21
	(v) an amino acid sequence consisting of amino acids 172 to 723 of SEQ ID NO:2;	p. 10, <i>ll.</i> 1-21
	(vi) an amino acid sequence consisting of amino acids 542 to 722 of SEQ ID NO:2;	p. 10, <i>ll.</i> 1-21
	(vii) an amino acid sequence consisting of amino acids 1-171 of SEQ ID NO:2;	p. 10, <i>ll.</i> 1-21
	(viii) an amino acid sequence consisting of amino acids 1-974 of SEQ ID NO:2;	p. 10, <i>ll.</i> 1-21
	(ix) an amino acid sequence consisting of amino acids 1-131 of SEQ ID NO:29;	p. 17, <i>ll.</i> 26-27 <sup>4</sup>
	(x) an amino acid sequence consisting of amino acids 680-939 of SEQ ID NO:29;	p. 17, <i>ll.</i> 26-27 <sup>5</sup>
	(xi) an amino acid sequence consisting of amino acids 940-1127 of SEQ ID NO:29;	p. 17, <i>ll.</i> 26-27 <sup>6</sup>
	(xii) an amino acid sequence consisting of amino acids 259-542 of SEQ ID NO:2;	p. 17, <i>ll.</i> 23-25 <sup>7</sup>
	(xiii) an amino acid sequence consisting of amino acids 172-259 of SEQ ID NO:2; or	p. 17, <i>ll.</i> 23-25 <sup>8</sup>
	(xiv) an amino acid sequence consisting of amino acids 722-974 of SEQ ID NO:2.	p. 17, <i>ll.</i> 23-25 <sup>9</sup>
141	The protein of any one of claims 135, 136, and 137, wherein the protein is non-naturally occurring.	p. 33, <i>ll.</i> 21-22

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<sup>4</sup> See footnote 3 above.

<sup>5</sup> See footnote 3 above.

<sup>6</sup> See footnote 3 above.

<sup>7</sup> See footnote 3 above.

<sup>8</sup> See footnote 3 above.

<sup>9</sup> See footnote 3 above.

No new matter has been introduced by these amendments. Claims 114-119 and 123-132, and 135-141 will be pending upon entry of the present amendments.

**1. THE OBJECTION TO THE CLAIMS SHOULD BE WITHDRAWN**

Claim 133 is rejected under 37 C.F.R. §1.75(c) because claim 133 is a multiple dependent claim that ultimately depends from another multiple dependent claim, namely claim 126. Claim 133 has been canceled, and new claim 138 has been added in its place. Claim 138 is an independent claim. Accordingly, the objection to claim 133 is obviated.

**2. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN**

**PRELIMINARY STATEMENT**

It appears that the Examiner based the rejections under 35 U.S.C. § 112, first paragraph, on the premise that Nogo proteins and fragments thereof that have not been shown to possess inhibitory activity in an NIH 3T3 fibroblast spreading assay have no utility (see Office Action of April 6, 2006 at, *e.g.*, p. 7, *ll.* 15-17). As discussed in more detail below, the specification discloses uses for these proteins and fragments that do not rely on such inhibitory activity. In particular, these proteins and fragments can be used to generate anti-Nogo antibodies. These antibodies, in turn, can be used for the identification of Nogo proteins, imaging of Nogo proteins, and biochemical analyses (detection and quantitation) of Nogo proteins, as detailed below.

It is noted that Nogo A and Nogo B displayed inhibitory activities in the NIH 3T3 fibroblast spreading assay (see specification Table 2, at page 68). The claimed Nogo A and Nogo B proteins are therefore useful by themselves.

The Examiner's position appears to be that even if Nogo proteins and fragments without neurite-outgrowth inhibitory activity can be used to generate anti-Nogo antibodies, these antibodies would be without utility because they are directed to proteins without utility. In response to this argument, Applicants direct the Examiner's attention to the genomic organization of the Nogo gene as depicted in Figure 1B. Three isoforms of Nogo are shown. Nogo A is composed of Exons 1, 2, and 3; Nogo B is composed of Exons 1 and 3; and

Nogo C is composed of only Exon 3, which it shares with the other Nogo isoforms. Thus, antibodies that are generated against Nogo C are expected also to bind to Nogo A and Nogo B, because these three isoforms have the amino acids encoded by Exon 3 in common. Consequently, antibodies against, *e.g.*, Nogo C, which was negative in the NIH 3T3 fibroblast spreading assay, should be useful to detect and quantitate Nogo A and Nogo B, both of which displayed inhibitory activity in the NIH 3T3 fibroblast spreading assay. Similarly, antibodies that were generated against Nogo protein fragments that lack inhibitory activity are still expected to bind to Nogo A, which has inhibitory activity. Consequently, such antibodies against Nogo fragments can be used to detect and quantitate Nogo A. Thus, Nogo fragments lacking inhibitory activity still have patentable use in generating antibodies to detect and quantitate Nogo isoforms with inhibitory activity.

Moreover, antibodies against regions of Nogo without inhibitory activity can be used in methods well known in the art to detect and measure only Nogo proteins having inhibitory activity. For example, such antibodies can be used in combination with antibodies that are specific to Nogo proteins that possess inhibitory activity. For example, all Nogo protein in a sample could be immunoprecipitated using an anti-Nogo C antibody. Subsequently, the Nogo A portion in the sample could be determined by Western blot analysis using an antibody that is specific to the amino acid sequence encoded by Exon 2 of the Nogo gene. Anti-Nogo C antibodies could also be used in assays such as sandwich ELISAs (in combination with another antibody specific to Nogo A or Nogo B) to detect only Nogo proteins that do have neurite outgrowth activity, as would be evident to the skilled artisan. Similarly, different anti-Nogo antibodies can be used in sequential purification procedures, such that, *e.g.*, anti-Nogo C is used to immunoprecipitate all Nogo protein from a sample, and subsequently anti-Nogo A is used to purify Nogo A from the Nogo proteins. As would be known by the skilled artisan, the benefit of such methods using a combination of antibodies is that the desired Nogo protein can be purified to a higher degree because contaminants that are due to cross-reaction with one antibody can be eliminated by subsequent purification with the other antibody.

To summarize, the claimed Nogo proteins and fragments, even those lacking neurite growth inhibitory activity, can be used to generate antibodies that are expected to bind to Nogo A. Additionally, Nogo C and its fragments can be used to generate antibodies that are expected to bind Nogo A and Nogo B. Thus, these antibodies are useful for the detection and quantitation of Nogo forms that have been shown to possess neurite outgrowth inhibitory

activity. Accordingly, the rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

## **2.1 THE REJECTION UNDER 35 USC § 112, FIRST PARAGRAPH, BASED ON NON-ENABLEMENT SHOULD BE WITHDRAWN**

Claims 114, 117, 120, and 122-137 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide enabling support for the use of residues 975-1163 of SEQ ID NO:2, residues 990-1178<sup>10</sup> of SEQ ID NO:29, SEQ ID NO:32 (rat Nogo C),<sup>11</sup> nucleic acids which hybridize under stringent conditions to Nogo protein-encoding nucleic acid according to claim 127 and 138,<sup>12</sup> and for the fragments of claims 134-137<sup>13</sup> that were either not active in the NIH 3T3 fibroblast spreading assay or that were not tested in this assay. Although not specified in paragraph 6 of the Office Action, on page 6 of the Office Action the Examiner appears to include claims 115, 116, 118, and 119 in the rejection. In particular, the Examiner argues that the claimed invention is useful only to the extent that the proteins of the invention actually inhibit spreading of 3T3 or PC12 cells. Because several claimed Nogo proteins and fragments thereof did not display inhibitory activity in the fibroblast spreading assay, it is argued in the Office Action, these embodiments are inoperative. Applicants respectfully disagree as set forth in detail below.

Before entry of the present amendment, claims 114, 117, 120, and 122 recited, *inter alia*, Nogo C.<sup>14</sup> The recitation of Nogo C has been deleted from claims 114 and 117. Claims

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<sup>10</sup> The recitation of "residues 990-1178" has been replaced in the claims with "the carboxy-terminal 188 amino acids" in the Amendment filed December 28, 2005. In order to more easily match Applicants' responses to the corresponding arguments in the Office Action, however, Applicants refer to "residues 990-1178" in the present response.

<sup>11</sup> Residues 975-1163 of SEQ ID NO:2, residues 990-1178 of SEQ ID NO:29, the carboxy-terminal 188 amino acids of SEQ ID NO:29, and SEQ ID NO:32 will be collectively referred to as Nogo C in this response.

<sup>12</sup> It is noted that new claim 138 replaces canceled claim 133.

<sup>13</sup> It is noted that claim 134 has been canceled.

<sup>14</sup> Residues 975-1163 of SEQ ID NO:2, residues 990-1178 of SEQ ID NO:29, the carboxy-terminal 188 amino acids of SEQ ID NO:29, and SEQ ID NO:32 will each be referred to as Nogo C in this response.

120 and 122 have been canceled. New claim 140, however, is directed, *inter alia*, to Nogo C. Applicants address the rejection of Nogo C first.

In their previous response, Applicants had pointed out that "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. § 2164.01(c) (Eighth Edition, Rev. 3, August 2005). The present specification discloses multiple uses, and the claims are not limited to a particular use. Thus, any enabled use of the claimed Nogo proteins and fragments is sufficient to defeat a rejection based on lack of enablement. In particular, Applicants had emphasized that the use of Nogo C as an immunogen for the generation of antibodies is enabled. In support, Applicants had provided evidence in form of hydrophilicity analyses according to Hopp and Woods indicating that antigenic determinant(s) predicted to confer immunogenicity are present in claimed proteins and fragments (see Exhibit C of the response of December 28, 2005).

The Examiner maintained the rejection because (1) antibodies directed to Nogo C would not be expected to block the inhibitory activity of Nogo; (2) the enabled use must "reasonably correlate with the entire scope of that claim;" and (3) Hopp and Woods, 1981, PNAS 78:3824 ("Hopp and Woods," attached as Exhibit E to the response of December 28, 2005) allegedly teaches that any six consecutive amino acids are antigenic.

Applicants will address each of the Examiner's above reasons in turn.

(1) The specification discloses multiple applications of anti-Nogo antibodies. Neutralization of Nogo-conferred neurite-outgrowth inhibitory activity is only one of the disclosed applications of anti-Nogo antibodies. Other applications are:

- (i) identification of Nogo proteins via expression cloning (p. 18, *ll.* 5-10);
- (ii) identification of Nogo proteins via adsorption to polysomes (p. 20, *ll.* 4-16);
- (iii) identification of Nogo proteins from other species (p. 28, l. 8);
- (iv) detection of the expression product of a Nogo gene (p. 19, l. 29 to p. 20, l. 3);
- (v) identification of expression vectors containing Nogo gene inserts (p. 23, l. 33 to p. 24, l. 11);
- (vi) imaging Nogo proteins (p. 29, *ll.* 27-30; p. 59, *ll.* 20-28);
- (vii) measuring levels of Nogo proteins in physiological samples (p. 29, *ll.* 27-30);

(viii) use in diagnostic methods (p. 51, l. 30 to p. 52, l. 16; p. 52, l. 26 to p. 53, l. 4);  
and

(ix) identification of Nogo-expressing cells (p. 60, ll. 11-20).

As discussed above in the Preliminary Statement, Nogo C includes Exon 3 of the Nogo gene, which is shared by all three isoforms of Nogo (see Figure 1B). Thus, antibodies directed to Nogo C are expected to cross-react with Nogo A and Nogo B. Thus, even assuming *arguendo* that the listed applications of anti-Nogo antibodies are ultimately only useful for Nogo proteins with neurite-outgrowth inhibitory activity, the anti-Nogo C antibodies are suitable for these applications because they are expected to bind to all isoforms of Nogo. These antibodies can be used in combination with isoform-specific anti-Nogo antibodies to detect, quantitate, and purify Nogo isoforms that inhibit NIH 3T3 fibroblast spreading. For example, these antibodies can be used in combination with Nogo-A or Nogo-B specific antibodies in a sandwich ELISA assay. For a more detailed discussion see the Preliminary Statement above.

(2) As discussed in Applicants' response of December 28, 2005, all the recited proteins and fragments are reasonably predicted to have uses as antigens/immunogens. Although some of the recited Nogo proteins and fragments have utilities in addition to antigenicity or immunogenicity, use as antigen/immunogen reasonably correlates with the entire scope of the claims.

(3) Hopp & Woods teaches that, for a given protein, the point of highest local average hydrophilicity in a protein is located in, or immediately adjacent to, an antigenic determinant. In order to locate the point of highest local average hydrophilicity Hopp & Woods used a sliding window of six amino acids. The average hydrophilicity values (Table 1) of the amino acids for each window were then plotted over the amino acid position of the window in the protein (see, *e.g.*, Figure 1). The plot shows the highest local average hydrophilicity, which correlates with antigenic determinants.

In their previous response, Applicants had identified the points of highest local average hydrophilicities for the following Nogo proteins: rat and human Nogo A, Nogo B, and Nogo C. These points are expected to be antigenic determinants. The Examiner is incorrect that Hopp & Woods teaches that any six consecutive amino acids are antigenic. Rather, Hopp & Woods teaches that the point of highest local average hydrophilicity is located in, or adjacent to, an antigenic determinant. Evidence of points of highest local

average hydrophilicities in the Nogo fragments as claimed in claims 135-137 is discussed below in the present response.

Regarding claims 115-116 and 118-119, the Examiner contends that the specification fails to teach how to use Nogo proteins/fragments without neurite-outgrowth inhibitory activity. In particular, the Examiner argues that the recitation of "wherein said protein has Nogo activity" is very broad. In order to clarify the claim language, claims 115-116 and 118-119 have been amended to recite that the claimed protein has one or more Nogo functional activities selected from the ability to bind to an anti-Nogo antibody; ability to generate an anti-Nogo antibody; ability to prevent regeneration of neurons in the spinal cord or brain; ability to confer to a substrate the property of restricting growth, spreading, and migration of neural cells; ability to inhibit dorsal root ganglia neurite outgrowth; ability to block NIH 3T3 cell spreading *in vitro*; and ability to block PC12 neurite outgrowth. Thus, it is clear that a protein with the required sequence identity and any one of the recited activities falls within the scope of these claims.

The Examiner further argues that, although these proteins/fragments can be used to generate anti-Nogo antibodies, these antibodies would not be expected to be useful because they are not expected to neutralize Nogo-conferred neurite-outgrowth inhibitory activity. Applicants respectfully disagree because anti-Nogo antibodies have many applications as set forth above. In particular, antibodies against any region of the Nogo gene can be used to detect and quantitate Nogo A, which has been shown to possess inhibitory activity in the NIH 3T3 fibroblast spreading assay.

Regarding claims 123-125, it is noted that these claims are dependent claims specifying that the claimed Nogo proteins are mammalian, human, or recombinant, respectively. Since the Examiner has not contended that these additional limitations are not enabled, it appears that claims 123-125 are rejected because they depend from rejected claims. As discussed above, the claims from which claims 123-125 depend are enabled. Thus, the rejection of claims 123-125 as non-enabled should be withdrawn.

Regarding claims 126-133, these claims, which are directed to nucleic acids encoding Nogo proteins, are rejected for the same reasons as the claims directed to Nogo proteins. It is noted that claim 133 has been canceled and claim 138 has been added in its place. Applicants assert that claims 126, and 128-132 are enabled because the claims directed to Nogo proteins are enabled as set forth above. Claims 127 and 138 are addressed below.

Claim 127 recites that the claimed nucleic acid comprises a polynucleotide that encodes a protein that displays inhibitory activity in an NIH 3T3 fibroblast spreading assay. Thus, by explicit claim language, the nucleic acids of claim 127 encode proteins that display inhibitory activity in an NIH 3T3 fibroblast spreading assay. The Examiner has acknowledged that Applicants have provided sufficient disclosure for how to use Nogo proteins with this inhibitory activity in a straightforward manner. Applicants have enabled the claimed Nogo proteins as discussed above. In particular, Applicants have enabled proteins and portions thereof having inhibitory activity in an NIH 3T3 fibroblast spreading assay. The nucleic acids that encode these proteins are therefore also enabled.

Claim 138 part (ii) recites that the claimed nucleic acid comprises a polynucleotide that encodes a protein that can be bound by an anti-rat or human Nogo A antibody. Because the protein encoded by the nucleic acid of claim 138 must react with such an anti-Nogo antibody, the protein encoded by a nucleic acid of claim 138 would be expected to be a suitable immunogen for the generation of anti-Nogo antibodies. As discussed above such antibodies can be used to detect and quantitate Nogo proteins that possess inhibitory activity in the NIH 3T3 fibroblast spreading assay.

Regarding claims 134-137, the Examiner argues that some of the Nogo fragments recited in these claims do not inhibit spreading of 3T3 or PC12 cells. Therefore, the Office Action alleges, the use of these Nogo fragments is not enabled. Applicants repeat their argument that these fragments can be used as antigens to generate anti-Nogo antibodies, which can be used as discussed above. Claim 134 has been canceled.

A hydrophilicity analysis, by way of example, has been performed essentially according to the method of Hopp and Woods (see Exhibit E of the Amendment of December 28, 2006) for the amino acid sequences specified in claims 135-137, as set forth in Exhibit A.<sup>15</sup> The hydrophilicity analyses were performed on July 8, 2005 and August 17, 2006, respectively, using an online service of the Expert Protein Analysis System proteomics server of the Swiss Institute of Bioinformatics (SIB) (URL: <http://us.expasy.org/tools/protscale.html>). For the online analysis, Hopp and Woods' amino acid scale and a window size of seven amino acids were selected. Print-outs of the hydrophilicity analyses are attached as Exhibit B. Points of highest local average

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<sup>15</sup> It is noted that several of the fragments that were formerly recited in claims 135 and 137 are now recited in new claims 139 and 140, respectively.

hydrophilicity can be seen throughout the amino acid sequence for all sequences as set forth in the Summary Of Nogo Hydrophilicity Analysis (Exhibit A), indicating that antigenic determinant(s), predicted to confer immunogenicity, are present in the claimed fragments. Thus, it is reasonably expected that the skilled artisan can use these fragments to generate anti-Nogo antibodies in accordance with the teachings of the application, see, *e.g.*, Section 5.5, beginning at page 28. Applicants reiterate that the claimed fragments are fragments of Nogo A protein. Consequently, antibodies directed against the fragments are expected to bind to Nogo A. These antibodies are therefore useful, *e.g.*, to detect and quantitate Nogo A, which has been shown to possess inhibitory activity in the NIH 3T3 fibroblast spreading assay.

Regarding claim 135, Applicants have deleted from claim 135 the recitation of the rat Nogo fragments other than the fragments that have been shown to inhibit spreading of 3T3 or PC12 cells (specification at p. 9, l. 36 to p. 10, l. 21; and Table 2, at p. 68) except for amino acid residues 623-640 of SEQ ID NO:2 and 762-1163 of SEQ ID NO:2. The recitations of amino acid residues 623-640 of SEQ ID NO:2 and 762-1163 of SEQ ID NO:2 have been retained in claim 135. The fragment of amino acids 762-1163 of SEQ ID NO:2 has been used as immunogen to generate the antiserum AS Bruna (specification at p. 59, ll. 6-10). Because AS Bruna neutralizes the inhibitory activity of Nogo A in an NIH 3T3 fibroblast spreading (see Figure 9A), the Nogo fragment against which this antiserum was raised is expected to have inhibitory activity in the NIH 3T3 fibroblast spreading. This data further shows that the region of amino acids 762-1163 of SEQ ID NO:2 is antigenic/immunogenic.

AS 472 was generated against the bovine peptide P472 (specification at p. 59, ll. 2-5). AS 472 neutralizes the inhibitory activity of Nogo A in an NIH 3T3 fibroblast spreading assay (see specification, Figure 9A). Consequently, the region of the Nogo protein against which AS 472 was raised, *i.e.*, P472, is expected to be necessary for Nogo A's inhibitory activity. P472 is the bovine Nogo sequence that corresponds to rat Nogo amino acids 623-640. With only three mismatches between the amino acid sequences of P472 and the corresponding rat fragment at amino acids 623-640 of SEQ ID NO:2, these two amino acid sequences are highly conserved. Accordingly, the rat Nogo fragment at amino acids 623-640 of SEQ ID NO:2 is likely to be necessary for Nogo A's inhibitory activity. The functional conservation of this region is confirmed by a cross-species experiment that is described in section 6.2.5 of the specification, beginning at page 66. The ability of rat neurites to regenerate in rat CNS tissue was investigated. AS 472 neutralized the inhibitory effect of the

CNS tissue thereby allowing the rat neurites to sprout new axons. Thus, the antibody against the bovine fragment appears to inhibit rat Nogo. Accordingly, the skilled artisan would expect that the epitope of P472 is also functionally conserved, and that therefore amino acids 623-640 of SEQ ID NO:2 are necessary for the inhibitory activity of Nogo. This cross-species experiment also demonstrates that the region of amino acids 623-640 of SEQ ID NO:2 is antigenic/immunogenic.

For the reasons set forth above, the rejections of claims 114-120 and 122-137 under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be withdrawn.

## **2.2 THE REJECTION UNDER 35 U.S.C. § 112 BASED ON LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN**

Claims 115-116, 118-119, 122-134, and 136 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Applicants respectfully disagree as set forth in detail below.

### **THE INSTANT SPECIFICATION PROVIDES SUFFICIENT WRITTEN DESCRIPTION FOR THE CLAIMS**

Claims 115-116, 118-119, 122-134, and 136 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide sufficient written description support for proteins with 90% and 95% sequence identity to the recited sequences. Applicants had argued in their response of December 28, 2005 that the written description for the genera of Nogo proteins meets the standard under 35 U.S.C. § 112, first paragraph, because the specification discloses that the proteins have (a) neurite outgrowth inhibitory activity; and/or (b) immunogenicity/antigenicity. The common structural elements that correlate with neurite outgrowth inhibitory activity are explicitly taught in the specification, the characteristics of common structural elements that correlate with immunogenicity/antigenicity are known to the skilled artisan and are taught in the specification (see page 27, lines 21-24; and page 28, lines 8-10) and thus can be readily identified by the skilled artisan.

In support of their argument that a common structural element is taught in the specification and/or could have been readily derived from the teachings of the specification by a skilled artisan at the time of filing of the application, Applicants (a) had previously

submitted hydrophilicity analyses for the claimed Nogo proteins and fragments in claims 115-116, 118-119, and 122 (Exhibit C to the response of December 28, 2005), and (b) submit concurrently hydrophilicity analyses for the claimed Nogo fragments in claim 136 (Exhibit A). Claims 122, 133, and 134 have been canceled. These hydrophilicity analyses demonstrate that the antigenic determinants of the claimed Nogo proteins are common structural elements that are taught in the specification.

In the Office Action dated April 6, 2006, the Examiner rejects Applicants' argument, contending that the ability of Nogo proteins/fragments to inhibit spreading in the NIH3T3 assay "is the only reasonable use for the claimed invention, the discussion of immunogenicity does not appear to be germane" (Office Action dated April 6, 2006, sentence spanning pages 8-9). As set forth above in the section addressing the enablement rejection, the specification discloses multiple uses for the claimed Nogo proteins/fragments based on their antigenicity/immunogenicity that are independent from inhibitory activity in the NIH3T3 fibroblast spreading assay. Even if antibodies against regions of Nogo without inhibitory activity are not expected to neutralize the inhibitory activity of Nogo proteins in the NIH 3T3 fibroblast spreading assay, these antibodies can still be used to locate, quantitate, and identify Nogo proteins, even those Nogo proteins with inhibitory activity. As detailed in the Preliminary Statement, antibodies against any region of the Nogo protein are also expected to bind to Nogo A because Nogo A is encoded by all three exons of the Nogo gene. Consequently, even antibodies that were generated using Nogo proteins or fragments without inhibitory activity can still be used to detect and quantitate a Nogo protein with inhibitory activity, such as Nogo A.

The Examiner argues that the specification does not disclose a representative number of species of proteins with 90% sequence identity to rat Nogo B, *i.e.*, amino acids 1-171 of SEQ ID NO:2 fused to amino acids 975-1163 of SEQ ID NO:2. Applicants assert that the skilled artisan could readily visualize a large number of species with at least 90% sequence identity to Nogo B wherein these sequences still display the antigenicity/immunogenicity of Nogo B. A hydrophilicity blot of Nogo B has been presented in the Amendment of December 28, 2006 (Exhibit C, Analysis No. 2). Points of greatest local hydrophilicity can be found throughout the protein, *e.g.*, around amino acid positions 45, 140, and 245. The skilled artisan could readily deduce sequences in which one or more of these regions of greatest local hydrophilicity are preserved to maintain the antigenicity/immunogenicity of the

protein but other parts are altered such that the resulting protein is 90% or more identical to Nogo B.

The Examiner argues that Nogo activity is defined in the specification to include neurite-outgrowth inhibitory activity and antigenicity and that the data obtained by NIH 3T3 fibroblast spreading assay (Table 2, p. 68) are not sufficient to show which regions are required for all Nogo activities. In response, Applicants point out that the structure-function analysis of Nogo as performed in Example 6.2.7, beginning at page 67, provides a correlation between the structure of the Nogo proteins and its neurite-outgrowth inhibitory activity. With regard to the activity of Nogo proteins as antigens, the specification teaches that a hydrophilicity analysis can be performed to identify the regions of Nogo that are hydrophilic (p. 27, *ll.* 21-24) and that such hydrophilic regions can be used as immunogens for antibody production (p. 28, *ll.* 8-10).

The Examiner has maintained the rejection of claims 123 and 124 for lack of written description because Applicants have not disclosed which features of the Nogo homologs make the proteins mammalian or human, respectively. Applicants respectfully disagree because the feature that makes a protein mammalian or human, respectively, is common knowledge in the art: a mammalian Nogo protein is encoded by a mammalian genome, and a human protein is encoded by a human genome.

Before entry of the present amendment, claims 125-132 depended from rejected claims. Since the Examiner has not rejected these dependent claims for lack of written description of the additional limitations recited in these claims, it appears that these claims are solely rejected because they depend from rejected claims. It is noted that claims 126-128 have been amended to incorporate limitations of the claims from which claims 126-128 depended such that claims 126-128 are now independent claims. The claims from which claims 125-132 depended are sufficiently supported by written description in the specification as discussed above. Thus, the rejection of claims 125-132 for lack of written description should also be withdrawn.

For the reasons set forth above the rejections of claim 115-116, 118-119, 123-132, and 136, under 35 U.S.C. § 112, first paragraph, for lack of written description, should be withdrawn.

Claim 117 and claims dependent thereon, namely claims 125-136, were rejected under 35 U.S.C. § 112, first paragraph, for lack of written description because there is no

literal support for the recitation of the claim language "the carboxy-terminal 188 amino acids of SEQ ID NO:29." In particular, the Examiner states that although support for "the carboxy-terminal 188 amino acids of Nogo A" is provided in the specification, Nogo A is not disclosed to be SEQ ID NO:29. Applicants point out that this recitation has been deleted from claim 117, and thus claim 117 and dependent claims 125-132 (claim 133 having been cancelled) do not contain new matter. However, the recitation now appears in new claim 140. New claim 140 does not contain new matter as discussed below.

It is well established that the law does not require that the specification provide support in exactly the same words as used in the claims to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. It is enough that the description conveys to one skilled in the art that the applicant had possession of the invention. For example, see *In re Wilder*, 736 F.2d 1516, 1520, 222 U.S.P.Q. 369, 372 (Fed. Cir. 1984):

It is not necessary that the claimed subject matter be described identically, but the disclosure originally filed must convey to those skilled in the art that applicant has invented the subject matter later claimed.

See also *Application of Lukach*, 442 F.2d 967, 969, 169 U.S.P.Q. 795, 796 (C.C.P.A. 1971): "[T]he invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of § 112."

New claim 140 does not contain new matter because this language is supported in the specification as filed at page 25, lines 19-21, in combination with other parts of the instant specification. The skilled artisan could readily derive from the present specification that human Nogo A is represented by the amino acid sequence of SEQ ID NO:29. Figure 1B shows the genomic organization of the Nogo gene. As shown therein, only Nogo A is encoded by exons 1, 2, and 3; Nogo B is encoded by exons 1 and 3; and Nogo C is encoded by exon 3. Exon 2 of the rat Nogo gene encodes amino acids 173-974 (specification at p. 12, lines 19-21; page 12, line 16; and Figure 1B<sup>16</sup>). Since exon 2 is unique to Nogo A, it would

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<sup>16</sup> As shown in Figure 1B, Nogo A and Nogo B share exon 1 and exon 3. At p. 12, lines 19-21, it is stated that Nogo B is composed of the amino terminal 172 amino acids and the carboxy terminal 188 amino acids of Nogo A. Thus, it would be clear to the skilled artisan that the amino terminal 172 amino acids of Nogo A are encoded by exon 1 and the carboxy terminal 188 amino acids of Nogo A by exon 3. The amino acid sequence between the amino terminal 172 amino acids and the carboxy terminal 188 amino acids of Nogo A consequently is encoded by exon 2. The beginning of the amino acid sequence encoded by exon 2 is thus amino acid 173. The end of the amino acid sequence encoded by exon 2 can be deduced by subtracting 188 amino acids from the total length of Nogo A. Since rat Nogo A is 1163 amino acids long (specification at p. 12, line 16), the first amino acid of the amino

be clear that Nogo A's from different species must contain a region that corresponds to amino acids 173-973 of rat Nogo A, *i.e.*, the region encoded by exon 2. Figure 13 shows an alignment between rat Nogo A and human Nogo.<sup>17</sup> As is apparent from the alignment in Figure 13, rat Nogo A is aligned over its entire length to the sequence of human Nogo, *i.e.*, the regions of rat Nogo A encoded by exons 1, 2, and 3 have counterparts in the human Nogo protein. In particular, amino acids 173-973 of rat Nogo A, which are encoded by exon 2, are aligned to a homologous portion of the human Nogo protein. Accordingly, the human Nogo sequence that is depicted in Figure 13 has the regions that correspond to the portions of rat Nogo A encoded by exons 1, 2, and 3. Since only Nogo A is encoded by all three exons, it is clear that the human Nogo protein depicted in Figure 13 is human Nogo A. A simple comparison of the human amino acid sequence shown in Figure 13 with SEQ ID NO:29 reveals that these sequences are identical. Thus, the specification clearly teaches that SEQ ID NO:29 represents the amino acid sequence of human Nogo A.

For the reasons set forth above the rejection of claim 117, under 35 U.S.C. § 112, first paragraph, for lack of written description, should be withdrawn.

Claims 134-136 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description support.

In particular, claim 134 has been rejected because there is no support for fragments at least 95% identical to the recited fragments. Solely to expedite prosecution, Applicants have canceled claim 134.

Claim 135 has been rejected because the Examiner could not find support for the recitation of residues 31-57 of SEQ ID NO:2, 11-191 of SEQ ID NO:32, 1090-1125 of SEQ ID NO:2, and 623-640 of SEQ ID NO:2. The recitation of fragments comprising amino acids 31-57 of SEQ ID NO:2, amino acids 11-191 of SEQ ID NO:32, and amino acids 1090-1125

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acid encoded by exon 3 is 975 (1163 minus 188). Thus, the last amino acid of the amino acid sequence encoded by exon 2 is 974.

<sup>17</sup> The incorrect recitation of SEQ ID NO:30 in the figure legend of Figure 13 was replaced with SEQ ID NO:29 in the amendment of October 21, 2002. Rat Nogo A is depicted in the bottom row of the alignment in Figure 13, as can be readily deduced from a comparison of the sequences in Figure 13 with the rat Nogo A sequence that is shown in Figure 2 (see also p. 12, *ll.* 13-18).

of SEQ ID NO:2 has been deleted from claim 135.<sup>18</sup> Support for the fragment comprising amino acids 623-640 of SEQ ID NO:2, can be found at page 59, lines 2-5, of the specification. This passage describes that the Antiserum 472 was generated against the bovine Nogo sequence P472. It is further stated that the amino acid sequence in rat Nogo A that corresponds to P472 is the amino acid sequence at 623 to 640 of SEQ ID NO:2. Although there are three mismatches between P472 and 623 to 640 of SEQ ID NO:2, the skilled artisan would recognize that the inventors had possession of the rat fragment because it is unambiguously identified by amino acid position in a disclosed sequence. Further, in view of the high degree of conservation between the bovine and rat fragments, the fact that AS472 neutralizes rat Nogo inhibitory activity (specification at p. 66, lines 2-3; and p. 66, line 28 to p. 67, line 4) indicates that the rat fragment has similar antigenic and neurite growth inhibitory properties as its bovine counterpart. Thus, the skilled artisan would recognize that the inventors had possession of the rat fragment of amino acids 623-640 of SEQ ID NO:2.

Claim 136 has been rejected because there is no support for fragments at least 95% identical to the recited fragments. Applicants disagree and direct the Examiner to p. 15, *l.* 18 to p. 16, *l.* 4, of the specification as filed. At p. 15, *ll.* 31-32, the specification discloses nucleic acids "encoding fragments of human Nogo protein having an amino acid sequence substantially similar to the amino acid sequence as shown in Figure 13," *i.e.*, SEQ ID NO:29. The term "substantially similar" is defined at p. 15, *l.* 36 to p. 16, *l.* 1, of the specification. In particular, it is stated that an amino acid is deemed substantially similar to a Nogo sequence if the sequence when more than 95% of the amino acid residues in the two molecules are identical. Accordingly, a fragment that is 95% identical to a human Nogo fragment is considered substantially similar to that human Nogo fragment, and such fragments are disclosed (p. 15, *ll.* 31-32). Thus, the skilled artisan could unambiguously derive from this disclosure that Applicants considered proteins with the recited degree of identity as part of the invention.

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<sup>18</sup> For completeness, it is noted that original claim 16 provides support for the fragments comprising amino acids 31-57 of SEQ ID NO:2, amino acids 11-191 of SEQ ID NO:32, and amino acids 1090-1125 of SEQ ID NO:2. The amendment of August 19, 2004 added the language of original claim 16 to the Summary of the Invention at p. 3, *l.* 28, so that support for these fragments can be found in this section of the specification.

For the reasons set forth above the rejections of claims 135 to 136, under 35 U.S.C. § 112, first paragraph, for lack of written description, should be withdrawn.

### **3. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN**

Claim 127 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because it recites the trademark Ficoll®. According to the U.S. Patent and Trademark Office's database (Trademark Electronic Search System; attached as Exhibit C), the trademark Ficoll® stands for copolymers of sucrose and epichlorohydrin that may be used to prepare high density solutions, for laboratory use. Claim 127 accordingly has been amended to recite "a copolymer of sucrose and epichlorohydrin" instead of Ficoll®.

It is noted that the Examiner stated that Ficoll is known as thiocyclam hydrogen oxalate according to a print-out from the Sigma website. Although ambiguous, it appears from the print-out provided by the Examiner that the chemical information relates to Pestanal®. However, the search result from the U.S.P.T.O. web site is clear—Ficoll® is the mark for copolymers of sucrose and epichlorohydrin.

Accordingly the rejection of claim 127 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

### **4. THE PRIOR ART-BASED REJECTIONS SHOULD BE WITHDRAWN PRIORITY**

The Examiner contends that the effective filing date for claim 117 and claims dependent thereon, namely claims 125-133, is September 24, 2001 because the recitation of "the carboxy-terminal 188 amino acids of SEQ ID NO:29" is allegedly new matter.<sup>19</sup> Applicants respectfully disagree.

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<sup>19</sup> In the Office Action of April 6, 2006, page 11, section 10, first sentence, the Examiner states that Applicants had argued that the effective filing date of all claims is November 6, 1998. This statement is inaccurate. In section 5a, beginning at page 28 of their response of December 28, 2005, Applicants discussed the effective filing date for claims 117-119 and 123-132 and concluded at page 29 that the effective filing date for claims 117-119 and 123-132 is November 6, 1998.

The present application is the national stage of international patent application no. PCT/US99/26160 filed November 5, 1999, which claims the benefit of U.S. Provisional Application No. 60/107,446 filed November 6, 1998 (the "Priority Application").

Applicants point out that the recitation of "the carboxy-terminal 188 amino acids of SEQ ID NO:29" has been deleted from claim 117. Since the Priority Application discloses and enables the subject matter of claim 117 and dependent claims 125-132 (claim 133 having been cancelled), these claims are entitled to an effective filing date of the Priority Application, *i.e.*, November 6, 1998. However, the recitation deleted from claim 117 now appears in new claim 140. New claim 140 is supported in the Priority Application at page 31, lines 23-26. Although this passage refers to Nogo A and not to SEQ ID NO:29, the skilled artisan could readily deduce from the Priority Application that human Nogo A is represented by the amino acid sequence of SEQ ID NO:29. Figure 1B of the Priority Application shows the genomic organization of the Nogo gene. As shown therein, only Nogo A is encoded by exons 1, 2, and 3; Nogo B is encoded by exons 1 and 3; and Nogo C is encoded by exon 3. Exon 2 of the rat Nogo gene encodes amino acids 173-973 (specification at p. 13, lines 15-19 of the Priority Application; page 13, line 13 of the Priority Application; and Figure 1B of the Priority Application<sup>20</sup>). Since exon 2 is unique to Nogo A, it would be clear that Nogo A's from different species must contain a region that corresponds to amino acids 173-973 of rat Nogo A, *i.e.*, the region encoded by exon 2. Figure 13 of the Priority Application shows an alignment between rat Nogo A and human Nogo.<sup>21</sup> As is apparent from the alignment in

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<sup>20</sup> As shown in Figure 1B of the Priority Application, Nogo A and Nogo B share exon 1 and exon 3. At p. 13, lines 15-19, of the Priority Application it is stated that Nogo B is composed of the amino terminal 172 amino acids and the carboxy terminal 188 amino acids of Nogo A. Thus, it would be clear to the skilled artisan that the amino terminal 172 amino acids of Nogo A are encoded by exon 1 and the carboxy terminal 188 amino acids of Nogo A by exon 3. The amino acid sequence between the amino terminal 172 amino acids and the carboxy terminal 188 amino acids of Nogo A consequently is encoded by exon 2. The beginning of the amino acid sequence encoded by exon 2 is thus amino acid 173. The end of the amino acid sequence encoded by exon 2 can be deduced by subtracting 188 amino acids from the total length of Nogo A. Since rat Nogo A is 1163 amino acids long (specification at p. 13, line 13, of the Priority Application), the first amino acid of the amino acid encoded by exon 3 is 975 (1163 minus 188). Thus, the last amino acid of the amino acid sequence encoded by exon 2 is 974.

<sup>21</sup> The incorrect recitation of SEQ ID NO:30 in the figure legend of Figure 13 of the present application has been replaced with SEQ ID NO:29 in the amendment of October 21, 2002. Rat Nogo A is depicted in the bottom row of the alignment in Figure 13 as can be readily deduced from a comparison of the sequences in Figure 13 with the rat Nogo A sequence that is shown in Figure 2 (see also p. 13, *ll.* 8-15, of the Priority Application).

Figure 13 of the Priority Application, rat Nogo A is aligned over its entire length to the sequence of human Nogo, *i.e.*, the regions of rat Nogo A encoded by exons 1, 2, and 3 have counterparts in the human Nogo protein. In particular, amino acids 173-973 of rat Nogo A, which are encoded by Exon 2, are aligned to a homologous portion of the human Nogo protein. Accordingly, the human Nogo sequence that is depicted in Figure 13 has the regions that correspond to the portions of rat Nogo A encoded by exons 1, 2, and 3. Since only Nogo A is encoded by all three exons, it is clear that the human Nogo protein depicted in Figure 13 is human Nogo A. A simple comparison of the human amino acid sequence shown in Figure 13 with SEQ ID NO:29 reveals that these sequences are identical. Thus, the specification of the Priority Application clearly teaches that SEQ ID NO:29 represents the amino acid sequence of human Nogo A. Therefore, new claim 140, which is directed to a fragment consisting of the carboxy-terminal 188 amino acids of SEQ ID NO:29, is entitled to the benefit of the priority date of November 6, 1998.

The Examiner further contends that the effective filing date for claims 134-136 is September 24, 2001 because new matter has allegedly been introduced as discussed above in connection with the written description support for the claimed invention. It is noted that claim 134 has been cancelled.

The Examiner argues that claim 135 recites new matter because the Examiner could not find support for the recitation of residues 31-57 of SEQ ID NO:2, 11-191 of SEQ ID NO:32, 1090-1125 of SEQ ID NO:2, and 623-640 of SEQ ID NO:2. The recitation of fragments comprising amino acids 31-57 of SEQ ID NO:2, amino acids 11-191 of SEQ ID NO:32, and amino acids 1090-1125 of SEQ ID NO:2 has been deleted from claim 135.<sup>22</sup> Support for the fragment comprising amino acids 623-640 of SEQ ID NO:2, can be found at page 79, lines 6-9, of the Priority Application (see also Figure 2a and page 6, line 22 to page 7, line 2, of the Priority Application). Antiserum 472 was generated against the bovine Nogo sequence P472, which corresponds to the amino acid sequence at positions 623 to 640 of SEQ ID NO:2. Although there are three mismatches between P472 and 623 to 640 of SEQ ID NO:2, the skilled artisan would recognize that the inventors had possession of the rat

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<sup>22</sup> For completeness, it is noted that original claim 16 provides support for the fragments comprising amino acids 31-57 of SEQ ID NO:2, amino acids 11-191 of SEQ ID NO:32, and amino acids 1090-1125 of SEQ ID NO:2. The amendment of August 19, 2004 added the language of original claim 16 to the Summary of the Invention at p. 3, l. 28, so that support for these fragments can be found in this section of the specification.

fragment because it is unambiguously identified by amino acid position in a disclosed sequence. Further, in view of the high degree of conservation between the bovine and rat fragments, the fact that AS472 neutralizes rat Nogo inhibitory activity (page 86, line 10, to page 87, line 8, of the Priority Application) indicates that the rat fragment has similar antigenic and neurite growth inhibitory properties as its bovine counterpart. Thus, based on the Priority Application, the skilled artisan would recognize that the inventors had possession of the rat fragment of amino acids 623-640 of SEQ ID NO:2. The effective filing date of the subject matter claimed in claim 135 is therefore November 6, 1998.

Claim 136 has been rejected because there is no support for fragments at least 95% identical to the recited fragments. Applicants disagree and direct the Examiner to p. 15, *l.* 18 to p. 16, *l.* 4, of the specification as filed. At p. 15, *ll.* 31-32, the specification discloses nucleic acids "encoding fragments of human Nogo protein having an amino acid sequence substantially similar to the amino acid sequence as shown in Figure 13," *i.e.*, SEQ ID NO:29. The term "substantially similar" is defined at p. 15, *l.* 36 to p. 16, *l.* 1 of the specification. In particular, it is stated that an amino acid is deemed substantially similar to a Nogo sequence if more than 95% of the amino acid residues in the two molecules are identical. Accordingly, a fragment that is 95% identical to a human Nogo fragment is considered substantially similar to that human Nogo fragment, and such fragments are disclosed. Thus, the skilled artisan could unambiguously derive from the specification as filed that Applicants considered proteins with the recited degree of identity as part of the invention. Consequently, the effective filing date of the subject matter claimed in claim 136 is November 5, 1999.

#### **4.1 MICHALOVICH DOES NOT ANTICIPATE CLAIMS 117 AND 125-132**

Claims 117 and 125-132 are rejected under 35 U.S.C. 102(e) as being allegedly anticipated by U.S. Patent Application Publication 2002/0010324 to Michalovich ("Michalovich").

Michalovich is a continuation application of U.S. Application serial no. 09/359,208 filed July 22, 1999. Michalovich further claims benefit of priority of two foreign applications, which were filed on July 22, 1998 and July 19, 1999, respectively. "Foreign applications' filing dates that are claimed . . . in applications, which have been published as U.S. or WIPO application publications or patented in the U.S., may not be used as 35 U.S.C. 102(e) dates for prior art purposes." M.P.E.P. § 2136.03(I). Thus, as conceded by the

Examiner, Michalovich is available as a reference under 35 U.S.C. 102(e) only as of July 22, 1999. Applicants' priority date of November 6, 1998 for claims 117 and 125-132 predates Michalovich. Thus, Michalovich is not available as prior art under 35 U.S.C. 102(e) against claims 117 and 125-132 and the rejection over Michalovich should be withdrawn.

#### **4.2 EISENBACH-SCHWARTZ IS NOT PRIOR ART AND THUS CANNOT ANTICIPATE CLAIMS 117-119 AND 123-127**

Claims 117, 125-127, and 134-135 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Application Publication 2002/0072493 by Eisenbach-Schwartz et al. ("Eisenbach-Schwartz").

The Examiner and Applicants agree that Eisenbach-Schwartz' effective date as a reference under 35 U.S.C. § 102(e) is June 28, 2001. However, the Examiner contends that claims 117, 125-127 and 134-135 are only entitled to the September 24, 2001 filing date of the present application and that Eisenbach-Schwartz is therefore prior art against these claims. Applicants respectfully disagree because, as set forth above, claim 117 and claims 125-127 dependent thereon are supported in the priority application and thus are entitled to an effective filing date of November 6, 1998.

The rejection of claim 134 under 35 U.S.C. § 102(e) is moot in view of the cancellation of this claim. As discussed above, the effective filing date of the subject matter claimed in claim 135 is November 6, 1998.

Because Eisenbach-Schwartz is not available as prior art against claims 117, 125-127, and 135, the rejection over Eisenbach-Schwartz should be withdrawn.

#### **4.3 AF132047 AND AB015639 ARE NOT PRIOR ART AND CANNOT ANTICIPATE CLAIMS 126-127**

Claims 126 and 127 are rejected under 35 U.S.C. § 102(b) over GenBank® entry at accession number AF132047 ("AF132047"). Claims 126 and 127 are also rejected under 35 U.S.C. § 102(b) over GenBank® entry at accession number AB015639 ("AB015639").

The publication dates of AF132047 and AB015639 are May 18, 1999 and September 3, 1999, respectively. Claims 126 and 127 are entitled to the priority date of November 6, 1998 as discussed above. Thus, because the effective filing date to which the rejected claims

are entitled predates the publication dates of AF132047 and AB015639, neither one of these GenBank® entries is prior art against the pending claims. Thus, the rejections should be withdrawn.

#### **4.4 THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN**

Claims 128-132 are rejected under 35 U.S.C. § 103(a) over AF132047 or AB015639 or Eisenbach-Schwartz, each in view of Schendel 1998 (Current Protocols in Molecular Biology 16.1.1 – 16.1.3; "Schendel").

#### **AF132047, AB015639, AND EISENBACH-SCHWARTZ ARE NOT PRIOR ART**

AF132047 and AB015639 are not prior art against claims 128-132. The publication dates of AF132047 and AB015639 are May 18, 1999 and September 3, 1999, respectively. As discussed above, claim 117 and the claims dependent thereon, including claims 128-132, are entitled to an effective filing date of the Priority Application, *i.e.*, November 6, 1998.

Eisenbach-Schwartz also is not prior art against claims 128-132. The Examiner and Applicants agree that Eisenbach-Schwartz' effective date as a reference is June 28, 2001. As discussed above, claim 117 and the claims dependent thereon, including claims 128-132, are entitled to an effective filing date of the Priority Application, *i.e.*, November 6, 1998.

Thus, AF132047, AB015639, and Eisenbach-Schwartz are not prior art against claims 128-132. The rejection of claims 128-132 under 35 U.S.C. § 103(a) over AF132047 or AB015639 or Eisenbach-Schwartz, each in view of Schendel, should therefore be withdrawn.

#### **5. THE NEW PRIOR ART-BASED REJECTIONS SHOULD BE WITHDRAWN**

##### **PRELIMINARY STATEMENT**

The Examiner's attention is directed to the enclosed Declaration of Prof. Martin E. Schwab under 37 C.F.R. § 1.132 ("Schwab Declaration"), which presents evidence that the claimed proteins are not disclosed in the references cited by the Examiner in the section entitled "New Rejections" on page 13 of the Office Action of April 6, 2006. Particularly, the Schwab Declaration demonstrates that the protein fractions described in these references were contaminated with CNS myelin material (see Schwab Declaration as discussed below).

In the event the Examiner disagrees, and to the extent that this rejection is based on facts within his personal knowledge, Applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 C.F.R. 1.104(d)(2).

## THE LEGAL STANDARD

Anticipation requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee. *Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F. 3d 299, 302 (Fed. Cir. 1995). An anticipating reference must describe and enable the claimed invention, including all the claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990); *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375 (Fed. Cir. 2002).

The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987): “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)(holding that “[t]he identical invention must be shown in as complete detail as is contained in the . . . claim”). Further, the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.* 75 F. 3d 1558 (Fed. Cir. 1996).

### **5.1 THE REJECTION UNDER 35 U.S.C. § 102 OVER CARONI SHOULD BE WITHDRAWN**

Claims 114, 116, 123, and 125 are rejected under 35 U.S.C. § 102(b) as anticipated by Caroni and Schwab, 1988, *Journal of Cell Biology*, 106:1281-1288 ("Caroni-1") as evidenced by Chen *et al.*, 2000, *Nature* 403:434-439 ("Chen-2") and Caroni and Schwab, 1998, *Neuron* 1:85-96 ("Caroni-2"). Applicants respectfully disagree because Caroni-1 does not teach all the limitations of the rejected claims.

Claims 114 and 116, and thus dependent claims 123 and 125, all specify that the claimed proteins are free of all CNS myelin material. Caroni-1, however, does not disclose

such a Nogo protein that is free of all central nervous system myelin material (Schwab Declaration, at ¶¶7-10), and thus cannot anticipate these claims. As described by Prof. Schwab:

In Caroni-1, we describe attempts to purify by conventional biochemical techniques the proteins that are responsible for the inhibitory substrate effect of rat CNS myelin on neurite outgrowth. Rat CNS myelin material was solubilized in sodium dodecyl sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) sample buffer and the myelin components were separated by SDS-PAGE (page 1285, left column, third paragraph). Subsequently, myelin proteins were extracted from gel regions corresponding to the migration distance of 35 kD and 250 kD proteins (page 1285, right column, first paragraph). As stated at page 1285 of Caroni-1 (the paragraph spanning the left and right columns and Figure 4), two protein fractions, namely a 35 kD fraction and a 250 kD fraction, with neurite outgrowth inhibitory activity were obtained by fractionating CNS myelin material using this purification procedure.

The 35 kD fraction and the 250 kD fraction resulting from the purification procedure of Caroni-1 were contaminated with central nervous system myelin material. As stated at page 1285 of Caroni-1, right column, lines 8-9, the regions of the SDS-PAGE gel from which these protein fractions were extracted contained more than one protein species.

We later attempted to use High Performance Liquid Chromatography (HPLC) to isolate individual proteins from the 35 kD fraction and 250 kD fraction for protein microsequencing. In the years between 1992 and 1994, we obtained short peptide sequences from the HPLC fractions. However, the peptide sequences obtained were only short and of insufficient quality to allow us to identify the novel protein. None of these peptide sequences obtained at that time from the HPLC fractions corresponded to the amino acid sequence of Nogo protein, which was determined later after the Nogo gene had been cloned. Thus, the HPLC fractions were of insufficient purity and contained a majority of myelin proteins other than Nogo protein. Thus, even if the HPLC purified material contained Nogo protein, any such Nogo protein could not have been free of all CNS myelin material.

Since the HPLC-purified material contained myelin proteins other than Nogo protein, the 35 kD and the 250 kD protein fractions from which the HPLC-purified material was obtained also contained myelin proteins other than Nogo protein.

(Schwab Declaration, at ¶¶7-10).

Thus, Caroni-1 does not teach Nogo protein that is free of all CNS myelin material. Because Caroni-1 does not teach all the limitations of the rejected claims, the rejection of

claims 114, 116, 123, and 125 under 35 U.S.C. § 102(b) as anticipated by Caroni-1 as evidenced by Chen-2 and Caroni-2 should be withdrawn.

## **5.2 THE REJECTION UNDER 35 U.S.C. § 102 OVER SPILLMANN SHOULD BE WITHDRAWN**

Claims 117-119, 123-125, and 136-137 are rejected under 35 U.S.C. § 102(b) as anticipated by Spillmann *et al.*, 1997, European Journal of Neuroscience, 9:549-555 ("Spillmann") as evidenced by Chen *et al.*, 2000, Nature 403:434-439 ("Chen-2").

Claims 117-119, 123-125, and 136-137 all specify that the claimed proteins are free of all CNS myelin material. Spillmann, however, does not disclose a Nogo protein that is free of all central nervous system myelin material (Schwab Declaration, at ¶¶17-19). As described by Prof. Schwab:

In Spillmann, we describe attempts to purify by conventional biochemical techniques the proteins that are responsible for the inhibitory substrate effect of human CNS myelin on neurite outgrowth. CNS myelin material was solubilized and the solubilized proteins were subsequently separated using SDS-PAGE (see sections "Preparation of myelin proteins" and "Gel analysis of inhibitory proteins from CNS myelin" at page 550 of Spillmann). Proteins were eluted from the 0-100, 100-200, and 200-300 kD regions of the SDS-PAGE gel (see section "Gel analysis of inhibitory proteins from CNS myelin" at page 550 of Spillmann). As stated at page 552 of Spillmann, the paragraph spanning the left and right columns, and the legend to Figure 3, only the protein fraction of proteins with molecular weights between 200 and 300 kD displayed neurite-outgrowth inhibitory activity.

The 200 kD to 300 kD fraction was contaminated with CNS myelin material. The proteins were obtained by eluting all CNS myelin proteins from the 200 kD to 300 kD region of an SDS-PAGE gel. Thus, numerous human CNS myelin proteins with a molecular weight between 200 kD and 300 kD should be present in this fraction. Any Nogo protein present in this fraction was therefore not free of all CNS myelin material.

Later attempts to sequence the proteins in the 200 kD to 300 kD fraction obtained by the above procedure failed to identify a Nogo protein due to the high level of contamination with CNS myelin proteins other than Nogo protein.

(Schwab Declaration, at ¶¶17-19).

Thus, Spillmann does not teach Nogo protein that is free of all CNS myelin material. Because Spillmann does not teach all the limitations of the rejected claims, the rejection of

claims 117-119, 123-125, and 136-137 are rejected under 35 U.S.C. § 102(b) as anticipated by Spillmann as evidenced by Chen-2 should be withdrawn.

**THE REJECTIONS UNDER 35 U.S.C. § 102 AND 35 U.S.C. § 103 OVER CARONI-1 OR CARONI-2 SHOULD BE WITHDRAWN**

Claims 114-116, 120, 122-123, 125, and 134-135<sup>23</sup> are rejected under 35 U.S.C. § 102(b) as anticipated by Caroni-1 or Caroni-2, or, in the alternative, these claims are rejected under 35 U.S.C. § 103(a) as obvious over Caroni-1 or Caroni-2. The rejection under 35 U.S.C. § 102(b) will be addressed first.

**THE ANTICIPATION REJECTION**

The claims are not anticipated by Caroni-1 essentially for the reason set forth in section 5.1 above. Briefly, claims 114-116, 123, 125, and 135 all specify that the claimed proteins are free of all CNS myelin material. In contrast, the protein fractions described in Caroni-1 are not free of all CNS myelin material as demonstrated by Prof. Schwab in the Declaration (Schwab Declaration, at ¶¶7-10). Thus, because Caroni-1 does not teach all the limitations of claims 114-116, 123, 125, and 135, Caroni-1 does not anticipate the rejected claims.

Caroni-2 does not anticipate the claims because Caroni-2 also fails to disclose any Nogo protein that is free of all central nervous system myelin material (Schwab Declaration, at ¶¶12-15). As described by Prof. Schwab:

We generated monoclonal antibodies against the 250 kD fraction and the 35 kD fraction, respectively, described in Caroni-1. The monoclonal antibodies were termed IN-1 and IN-2 (see Abstract of Caroni-2). We attempted to use IN-1 in an immunoprecipitation to isolate inhibitory proteins from CNS myelin using two different protocols (see Caroni-2, pages 89-91, and 95 (third paragraph); legend of Table 4). Briefly, in Protocol 1, solubilized CNS myelin protein was incubated with IN-1. In Protocol 2, IN-1 antibody was incubated with intact myelin membranes, and antigen-antibody complexes were subsequently solubilized. In both protocols, rabbit anti-mouse antibodies and *S. aureus* cells were used to sediment the antigen-antibody complexes. Dissociation of the antigen-antibody complexes that were obtained using both protocols, by elution of the antigen,

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<sup>23</sup> It is noted that claims 120, 122, and 134 have been canceled by the present Amendment.

acetone precipitation, and reconstitution into liposomes, yielded proteins with inhibitory activity. Additionally, IN-1 immunoprecipitated protein from Protocol 2 was separated by SDS-PAGE and gel regions corresponding to 35 kD and 250 kD molecular weights were extracted and reconstituted into liposomes (Table 4 and legend of Table 4, at page 91).

The material immunoprecipitated by IN-1 and recovered in Protocol 1 and Protocol 2 was not free of all CNS myelin material. When we conducted Western blot analysis of CNS myelin material using IN-1 (see Figure 5 of Caroni-2), IN-1 reactive bands of molecular weights other than the molecular weights of 35 kD and 250 kD were observed. Moreover, when proteins immunoprecipitated by IN-1 were separated by SDS-PAGE, multiple protein bands of molecular weights other than the molecular weights of the 35 kD and the 250 kD fractions were observed. Thus, the material that was immunoprecipitated with IN-1 antibody contained myelin proteins other than Nogo protein because of the ability of IN-1 to bind to proteins other than Nogo protein.

IN-1 is an IgM antibody. The material that was obtained by immunoprecipitation using IN-1 and subsequent gel extraction could not be expected to be pure using an IgM as the precipitating antibody, since IgM antibodies are commonly known to display nonspecific binding (see, *e.g.*, page 56, second full paragraph, of Epstein, 1994, FDA Regulation of HIV-Related Tests and Procedures, In: AIDS Testing-A Comprehensive Guide to Technical, Medical, Social, Legal, and Management Issues, Eds. Schochetman and George, 2<sup>nd</sup> ed., Springer, New York; attached as Exhibit 4). The material was not free of all CNS myelin material as later shown in my laboratory by SDS-PAGE analysis (data not shown in Caroni-2).

In Caroni-2, IN-2 was shown to bind to CNS myelin inhibitory substrates and to neutralize their non-permissive substrate properties (Caroni-2, at page 89, left column, and Table 3 at page 91). IN-2 was not used in immunoprecipitation experiments in Caroni-2. Caroni-2 shows that IN-2 also recognizes proteins other than inhibitory proteins, such as cytoskeleton-associated antigens from astrocytes (Caroni-2, at page 89, left column). In subsequent experiments in my laboratory, we observed that IN-2 reacts with intermediate filaments (glial fibrillary acidic protein (GFAP) and neurofilaments in the CNS). In a Western blot analysis of CNS material that had been separated by one- or two-dimensional SDS-PAGE, the IN-2 antibody detected bands/spots of the size and charge of neurofilament and GFAP (B. Rubin, PhD Thesis, University of Zurich, 1995). Thus, immunoprecipitates of CNS myelin material using IN-2 would be contaminated with other proteins such as neurofilament.

(Schwab Declaration, at ¶¶12-15). Thus, because Caroni-2 does not teach all the limitations of claims 114-116, 123, 125, and 135, Caroni-2 does not anticipate the rejected claims.

## THE OBVIOUSNESS REJECTION

Claims 114-116, 123, 125, and 135 are rejected under 35 U.S.C. 103(a) as being made obvious by Caroni-1 or Caroni-2.

### The Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The case law makes clear that the requirement for a showing of a teaching or motivation to combine prior art references is needed to prevent reliance on impermissible hindsight-based obviousness analysis. See *In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002)(quoting *In re Dembiczak*, 175 F.3d 994, 999, (Fed. Cir. 1999)). “[T]he Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” *Id.* (quoting *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992)(internal quotations omitted).

### Caroni-1 Or Caroni-2 Do Not Teach All Claim Limitations

Claims 114-116, 123, 125, and 135 all specify that the claimed proteins are free of all CNS myelin material. In contrast, neither Caroni-1 nor Caroni-2 teaches Nogo protein that is free of all CNS myelin material (Schwab Declaration, at ¶¶7-10 and 12-15). It is not apparent from the Office Action dated April 6, 2006 whether the rejection was made over Caroni-1 and Caroni-2 individually or in combination. In particular, the Office Action stated “as obvious over Caroni (1988a), Caroni (1988b).” Nevertheless, even if the Examiner had combined Caroni-1 and Caroni-2, the combination of these two references would still not disclose Nogo protein that is free of all CNS myelin material. Further, neither Caroni-1 or Caroni-2 or the combination of these references provides a reasonable expectation of success of obtaining Nogo protein that is free of all CNS myelin material.

Prof. Schwab stated in his Declaration:

[C]onventional biochemical techniques are insufficient to obtain Nogo protein pure enough for protein sequencing. In fact, it took almost ten years for my laboratory to develop a purification procedure capable of yielding sequencing-grade Nogo protein, and I am aware that several competing laboratories failed in their attempts to purify Nogo protein.

(Schwab Declaration, at ¶23). A detailed discussion of the failure of Caroni-1 and Caroni-2 to obtain sequencing-grade Nogo protein can also be found in the Schwab Declaration at paragraphs 7 to 10 and 12 to 15, respectively. Thus, it was not possible to obtain sequencing-grade Nogo protein by routine biochemical techniques, due to contamination of the Nogo protein with CNS myelin material. The difficulty associated with the purification of Nogo protein demonstrates that there could not have been a reasonable expectation of success to purify the Nogo protein to such a degree that it would be free of all CNS myelin material.

Thus, because not all the limitations of the rejected claims are suggested by the cited prior art with a reasonable expectation of success in obtaining the claimed subject matter, the rejection of claims 114-116, 123, 125, and 135 under 35 U.S.C. 103(a) as obvious by Caroni-1 or Caroni-2 should be withdrawn.

#### **THE REJECTIONS UNDER 35 U.S.C. § 102(b) OVER CHEN-1 SHOULD BE WITHDRAWN**

Claim 127 is rejected under 35 U.S.C. § 102(b) as anticipated by the abstract entitled "Molecular Cloning of a Gene for a Putative Inhibitor to CNS Regeneration" by Chen *et al.* for the 27<sup>th</sup> Annual Meeting of the Society for Neuroscience, 1997 ("Chen-1"), and evidenced by Chen-2.

The abstract by Chen *et al.* accompanied a poster that was presented at the 27<sup>th</sup> Annual Meeting of the Society for Neuroscience (Schwab Declaration, at ¶¶20).

#### **CHEN-1 DOES NOT ENABLE THE CLAIMED SUBJECT MATTER**

The case law requires that for a reference to be anticipatory, the reference must enable the claimed invention: "the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries, Inc. v. Guardian Industries Corp.* 75 F. 3d 1558 (Fed. Cir. 1996). In contrast, the information provided in Chen-1 is insufficient to obtain the nucleic acids that are claimed in claim 127 without undue experimentation. As discussed by Prof. Schwab:

Chen-1 lists three cDNA clones: EST(rat), Oli18(rat), and CWP1-

3(bovine). Chen-1 also states that, based on Northern blot analyses, the gene corresponding to these cDNA clones likely encodes three different transcripts. These cDNA clones were later shown to represent partial sequences of the Nogo gene.

Chen-1, and the related poster, did not disclose any nucleotide or protein sequences of Nogo. Without this sequence information, it would have required extensive experimentation to obtain the nucleic acids that encode the Nogo proteins. For example, to employ the method suggested by Chen, first, it would have been necessary to obtain Nogo protein pure enough for protein sequencing. Second, degenerate oligonucleotides would have had to be designed based on the protein sequence to screen cDNA libraries.

The first step listed in paragraph 22 requires more than routine experimentation. As evidenced by my discussion of Caroni-1, Caroni-2, and Spillmann hereinabove, conventional biochemical techniques are insufficient to obtain Nogo protein pure enough for protein sequencing. In fact, it took almost ten years for my laboratory to develop a purification procedure capable of yielding sequencing-grade Nogo protein, and I am aware that several competing laboratories failed in their attempts to purify Nogo protein.

Successful implementation of the second step listed in paragraph 22 to obtain a Nogo cDNA also requires more than routine experimentation. Because the oligonucleotide sequences that are designed based on the peptide sequences are degenerate, only a small subset of oligonucleotides will be complementary to Nogo cDNA sequences. Consequently, detection of a cDNA in a cDNA library using these degenerate probes is more difficult and less predictable than screening of a cDNA library using traditional probes. When my laboratory ultimately carried out this method, we had to perform several rounds of cDNA screens to obtain the full length cDNA because of the considerable length of the Nogo gene. In fact, we had to use several partial cDNA sequences to assemble the full length cDNA. In addition, it proved very difficult to obtain cDNA clones encoding the amino terminal portion of Nogo A and Nogo B. To overcome these difficulties, we used the sequences of the originally isolated cDNA clones that encoded the carboxy terminal portion of Nogo to search for EST sequences in a publicly available database. Subsequently, we used the EST sequences to design new probes to perform additional cDNA screens. This strategy allowed us finally to obtain cDNA clones encoding the amino terminal portion of Nogo A and Nogo B proteins. Thus, it would have taken extensive experimentation based upon the disclosure of Chen-1 to obtain full-length cDNA sequences encoding rat and/or human protein.

(Schwab Declaration, at ¶¶21-24). Because undue experimentation would be required to obtain the claimed nucleic acids based on the information disclosed in Chen-1, Chen-1 does not anticipate claim 127. Thus, the rejection under 35 U.S.C. § 102(b) over Chen-1 should be withdrawn.

**THE REJECTIONS UNDER 35 U.S.C. § 103(a) OVER CHEN-1 SHOULD BE WITHDRAWN**

Claims 127-132<sup>24</sup> are rejected under 35 U.S.C. § 103(a) over Chen-1 and Sambrook (1989, *Molecular Cloning*, pages 16.3 to 16.22 and 17.3 to 17.9; "Sambrook") and Bregman *et al.*, 1995 (*Nature* 378:498-501; "Bregman"). In particular, the Examiner argues that there would have been motivation provided by Bregman to insert the nucleic acids taught in Chen-1 into vectors and host cells and produce proteins, and that these methods were available to the skilled artisan as evidenced by Sambrook.

Prof. Schwab discusses in his declaration at paragraphs 23 and 24 the difficulties associated with obtaining sequencing-grade Nogo protein and ultimately Nogo-encoding nucleic acids.

[C]onventional biochemical techniques are insufficient to obtain Nogo protein pure enough for protein sequencing. In fact, it took almost ten years for my laboratory to develop a purification procedure capable of yielding sequencing-grade Nogo protein, and I am aware that several competing laboratories failed in their attempts to purify Nogo protein.

...

Because the oligonucleotide sequences that are designed based on the peptide sequences are degenerate, only a small subset of oligonucleotides will be complementary to Nogo cDNA sequences. Consequently, detection of a cDNA in a cDNA library using these degenerate probes is more difficult and less predictable than screening of a cDNA library using traditional probes. When my laboratory ultimately carried out this method, we had to perform several rounds of cDNA screens to obtain the full length cDNA because of the considerable length of the Nogo gene. In fact, we had to use several partial cDNA sequences to assemble the full length cDNA. In addition, it proved very difficult to obtain cDNA clones encoding the amino terminal portion of Nogo A and Nogo B. To overcome these difficulties, we used the sequences of the originally isolated cDNA clones that encoded the carboxy terminal portion of Nogo to search for EST sequences in a publicly available database. Subsequently, we used the EST sequences to design new probes to perform additional cDNA screens. This strategy allowed us finally to obtain cDNA clones encoding the amino terminal portion of Nogo A and Nogo B proteins. Thus, it would have taken extensive experimentation based upon the

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<sup>24</sup> This obviousness rejection is based on the Examiner's conclusion that Chen-1 anticipates claim 127. No further argument is made that the combination of Chen-1 with Sambrook and Bregman makes claim 127 obvious.

disclosure of Chen-1 to obtain full-length cDNA sequences encoding rat and/or human protein.

(Schwab Declaration, at ¶¶21-24). Neither Sambrook nor Bregman discloses any information that would have facilitated the purification of Nogo protein or the cloning of the Nogo-encoding nucleotide sequences. Sambrook is concerned merely with routine methods for expressing proteins that are already cloned. Bregman reports a therapeutic application of an anti-Nogo antibody, namely the recovery of neuronal functions after spinal cord injury by application of the IN-1 antibody.

The difficulties associated with the purification of Nogo protein and the cloning of Nogo-encoding nucleic acids demonstrate that the references cited by the Examiner could not provide one of ordinary skill with a reasonable expectation of success to obtain the Nogo-encoding nucleotide sequences. Because these sequences are essential elements of the claimed vectors and host cells, there is also no reasonable expectation of success of obtaining these vectors and host cells.

Thus, because none of the cited references individually or in combination provides a reasonable expectation of success to obtain the claimed nucleic acids, vectors, and host cells, the rejection under 35 U.S.C. § 103(a) over Chen-1, Sambrook, and Bregman should be withdrawn.

### CONCLUSION

Applicants respectfully request that the present remarks and amendments be entered and made of record in the instant application. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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